683 TYPE-I-INTERFERON ACTIVATES CROSS-DRESSED CD11B$^+$CONVENTIONAL DENDRITIC CELLS TO ENHANCE ANTI-TUMOR IMMUNITY

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Background Conventional dendritic cells (cDC) are critical mediators of protective anti-tumor CD8$^+$ T-cell responses.[1] Batf3-driven DC1 are the predominant cDC subset driving anti-tumor immunity due to their specialized ability to cross-present antigens for T-cell activation.[2–4] However, the contribution of other tumor-infiltrating DC subsets such as CD11b$^+$ DC2 to anti-tumor immunity remains poorly characterized. Recent studies suggest that under inflammation, DC subsets can exist in various functional states with differential impacts on their stimulatory potential.[5–7] In this study, we sought to dissect the contributions of distinct DC states during a productive or dysfunctional anti-tumor immune response. A nuanced understanding of DC activation states in tumors and the signals that drive them carries therapeutic potential to modulate anti-tumor immunity and enhance immunotherapy responses.

Methods We compared the DC infiltrate of a regressing tumor and a progressing tumor to study DC states. Flow immunophenotyping and RNA-sequencing was performed to profile the intratumoral DC compartment. Sorted DC subsets were co-cultured with T-cells ex vivo to evaluate their stimulatory capacity. Cross-dressing (*in vivo*/*ex vivo*) was assayed by staining for transfer of tumor-derived H-2^b MHC complexes to MHC-mismatched or β2M-deficient DC.

Results Anti-tumor CD8$^+$ T-cell responses in Batf3$^{-/-}$ mice lacking DC1 were maintained in regressor tumors but not progressor tumors, suggesting DC1-independent anti-tumor immunity. Functional assays and RNA-sequencing of the intratumoral DC compartment of regressor tumors revealed a Zbtb46-dependent CD11b$^+$ cDC activation state expressing an interferon-stimulated gene signature (ISG$^+$ DC) that was critical for driving optimal anti-tumor CD8$^+$ T-cell responses. Sorted ISG$^+$ DC could activate CD8$^+$ T-cells similar to DC1. Unlike cross-presenting DC1, however, ISG$^+$ DC acquired antigens by cross-dressing with tumor-derived peptide-MHC, thereby bypassing the requirement for cross-presentation to initiate CD8$^+$ T-cell-immunity. Interestingly, ISG$^+$ DC were enriched in regressor tumors compared to progressor tumors, and this was attributable to constitutive tumor cell-intrinsic type-I-interferon (IFN-I) production in regressor tumors. Ablation of tumor cell-derived IFN-I in regressor tumors led to complete loss of anti-tumor T-cell responses in Batf3$^{-/-}$ mice. Conversely, addition of IFNβ to progressor tumors induced ISG$^+$ DC and rescued anti-tumor T-cell responses in Batf3$^{-/-}$ mice.

Conclusions We identified a novel IFN-I-induced activation state of CD11b$^+$ cDC, called ISG$^+$ DC, that was capable of driving anti-tumor CD8$^+$ T cell immunity by cross-dressing with tumor-derived pMHC complexes in the absence of DC1. Engaging additional functional states of DC, such as ISG$^+$ DC, will strengthen anti-tumor immunity and may improve immunotherapy responses.

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